SOUTH AUSTRALIAN MATERNAL SERUM ANTENATAL SCREENING (SAMSAS©) PROGRAM


Robert Cocciolone,
Head, Antenatal Screening, WCH Genetics & Molecular Pathology Directorate, SA Pathology
“providing obstetric support”
Longest running program in Australia,
-1978 Neural Tube Defect (NTD) screening
-1990/91 Down syndrome & other pregnancy pathologies (15-20wks)
-June 2001 First Trimester Down syndrome screening (10-14wks)
-April 2009 Integrated Testing in Second Trimester (9-20wks)

Develop and manage own software and algorithms
Service SA, TAS, NT with screening service support to PMH in WA
Integrated with Neonatal Screening database
Electronic access to Cytogenetic and Ultrasound reports
Yearly audits published in the SA Birth Defects Register Report
www.wch.sa.gov.au

- Services
- A for Antenatal Screening or
- B for Birth Defects Register
- Google SAMSAS
Maternal Serum Screening Test
Down Syndrome, Neural Tube Defects and other Pregnancy Pathologies

All Enquiries (08) 8161 7285
SA Pathology at the Women’s & Children’s Hospital
A9A
Fax (08) 8161 8085 samsas.program@health.sa.gov.au

Family Name

Given Names

Date of Birth / / UR No

Address

Postcode

Medicare Number

Ethnic Group:
[] Caucasian [ ] Aboriginal [ ] South Asian [ ] Oriental [ ] Afro-Caribbean

Patient status at time of the service or specimen collected
[ ] Yes [ ] No

Private patient in a private hospital or approved day hospital facility
[ ]

Private patient in a recognised hospital
[ ]

Medicare (public) patient in a recognised hospital
[ ]

Outpatient of a recognised hospital
[ ]

Requesting Doctor (Surname & initials, address, Tel/Fax/email, Provider No.)

First Trimester Screen [ ] Second Trimester [ ] Neural Tube only [ ]

Cycle Length days Maternal weight kgs

EDD/LMP / / Certain? [ ] Yes [ ] No [ ]

GA Clinical weeks + days on / / [ ]

GA Ultrasound weeks + days on / / [ ]

Crown-rump length (CRL) mm on / / [ ]

Nuchal Translucency mm on / / [ ]

Pregnancy Complications:
[] Twins [ ] Triplets

[ ] IVF Age Donor egg [ ]

[ ] Diabetes (IDDM only) [ ] Smoker [ ] Previous [ ] T21 [ ] T18/13 [ ] Other

Name of Imaging Practice:
For first trimester screening an Ultrasound request form is required for Nuchal Translucency, 11-13w6d.

Signature

Request Date / /

Copies of report to (Name, address)

Medicare Benefits (Section 26A of the Health Insurance Act 1973)
[] Not for public Health System distribution

5-10ml CLOTTED BLOOD SAMPLE
Gel or plain tube - no anticoagulant

Privacy Disclosure
SAMSAS recognises the personal information contained in this document - with the purpose of Risk assessment and Program Audits. SAMSAS may therefore request copies of ultrasound and cytogenetic reports.
<table>
<thead>
<tr>
<th>Lab. Number</th>
<th>SAMSAS form</th>
<th>Group</th>
<th>Previous Labno</th>
<th>Notes</th>
<th>Results</th>
<th>Doctors</th>
<th>Reports</th>
<th>Outcome</th>
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<td>P.C.</td>
<td>Referring Lab. LAN</td>
<td>GGG No</td>
<td>NT Provider</td>
<td>TDS</td>
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<td>F7 = New Dr</td>
<td>Sample Date</td>
<td>Sample Type</td>
<td>Appearance</td>
<td>Weight</td>
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<td>EDD by U/s</td>
<td>GA Clinical</td>
<td>GA Ultrasound</td>
<td>CRL</td>
<td>GA Var. Flag</td>
<td>FT-Rep. MoMs Only</td>
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MSS is offered as a program with access to pre & post test information, genetic counselling and diagnostic services – cvs, amnio & ultrasound.

Pre-test information for parents

Screening for Neural Tube Defect, Down syndrome and Trisomy 18

What is screening for Neural Tube Defects, Down syndrome and Trisomy 18?

For most parents, pregnancy ends with the birth of a normal healthy baby. In a small number of pregnancies, the baby develops with a serious problem. Neural Tube Defects, Down syndrome and Trisomy 18 are serious abnormalities that occur early in the development of a baby. It is not known why they happen.

Some tests you can have during pregnancy, which can show whether or not your baby has increased risk for one of these problems. You do not have to have these tests and some women choose not to have them. Before deciding if you want these tests, you should understand what the abnormality means, what the tests actually mean, and what the results might mean for you and your family.

What are Neural Tube Defects, Down syndrome and Trisomy 18?

Neural Tube Defects are serious abnormalities which happen during the development of the brain and spinal cord in about 1 in 1000 babies. It is not known why this happens. There are two main types: anencephaly and spina bifida. In anencephaly there is abnormal development of the baby's brain and skull. Babies with anencephaly usually die soon after birth. In spina bifida the baby's spine does not close properly. Babies with spina bifida may have paralysis of the legs, lack of bladder and bowel control, and curvature of the spine. Hydrocephalus (too much fluid around the brain) can also occur.

For more information about spina bifida contact:
The Spina Bifida and Hydrocephalus Association of South Australia (08) 8364 5900 www.spina-bifida-sa.org
Spina Bifida Association of Tasmania (03) 6275 9997

Down syndrome and Trisomy 18 are chromosomal abnormalities. Risks with Down syndrome have an extra chromosome 21 and those with Trisomy 18 have an extra chromosome 18. About 1 in 850 babies has Down syndrome and 1 in 3000 babies has Trisomy 18. Children with Down syndrome have varying levels of intellectual disability and a characteristic appearance. They may have medical problems involving their heart, bowel and thyroid gland. Some may have problems with sleeping and feeding. With medical treatment and social support, children with Down syndrome will usually grow up to be good health and with a reasonable quality of life.

For more information about Down syndrome contact:
The Down Syndrome Society of South Australia (08) 8365 3510 www.downsinfo.org.au
Down Syndrome Association of Tasmania (03) 6224 0490

Trisomy 18 is usually fatal. 90% of affected pregnancies fail before term. Of the 10% reaching term, half will not survive the first week and most will not survive the first year. Children with Trisomy 18 have serious intellectual disability.

What are the tests?

Between 19 and 20 weeks of pregnancy you may be offered screening tests to look for abnormalities in your baby. Check which tests are available through your local hospital clinic. The screening tests are a first step in finding out whether or not your baby might have an abnormality. It is important for you to know that these screening tests can give you a definite yes/no answer to the question ‘Does my baby have a problem’? They can only show if there is a chance that your baby might have an abnormality.

The tests are a blood test and an ultrasound scan.

The blood test is done on a small sample (5 ml) of your blood. Your doctor will arrange for this to be taken. There are no known dangers to you or your pregnancy in going this blood sample.

You will then attend an appointment with the ultrasound imaging for the ultrasound scan. Your doctor will arrange this for you. Ultrasound scanning is a way of testing your baby’s organs and bones. There are no known dangers to you or your baby in this type of ultrasound scan.

What can the tests tell?

If you are between 19 and 14 weeks pregnant, the blood test and the ultrasound scan used together can show if there is a greater than expected chance (an increased risk) that your baby might have Down syndrome or Trisomy 18. If you are between 14 and 20 weeks pregnant, the blood test can show if there is a greater than expected chance (an increased risk) that your baby might have Down syndrome, Trisomy 18 or a Neural Tube Defect.

About 95% of women who have these screening tests receive a report stating your baby is not at increased risk of having an abnormality. A smaller number (5% or 1 in 20) will receive a report stating there is an increased risk of an abnormality in your baby.

What do ‘increased risk’ and ‘not at increased risk’ mean?

If you received a screening test report which says your baby is not at increased risk it means there is only a very small chance that your baby has a neural tube defect, Down syndrome or Trisomy 18.

If you received a screening test report which says your baby is at increased risk then you should be aware that there is a possibility of an abnormality in your baby.

If you received a screening test report which says your baby is at increased risk you should be aware that there is a possibility of an abnormality in your baby.

“increased risk of Neural Tube Defect”

What does it mean?

Information from the South Australian Maternal Serum Screening (SAMS) Program, SA Pathology at Women’s and Children’s Hospital, North Adelaide 1999

“increased risk of Down Syndrome”

What does it mean?

Information from the South Australian Maternal Serum Screening (SAMS) Program, SA Pathology at Women’s and Children’s Hospital, North Adelaide 1999

“increased risk of Trisomy 18 (Edwards syndrome)”

What does it mean?

Information from the South Australian Maternal Serum Screening (SAMS) Program, SA Pathology at Women’s and Children’s Hospital, North Adelaide 1999

Is there something wrong with my baby?

Everybody who receives a maternal serum screening report saying ‘Trisomy 18 increased risk straight away asks’ ‘is there something wrong with my baby?’ At this stage the only answer that can be given is ‘probably not, but we should check it again’.

95% of women who receive a report like this go on to have a normal healthy baby.

Why have I got this report?

We have performed a screening test which is designed to tell if there is a greater than expected chance (an increased risk) your baby might have Trisomy 18.

Your results indicate there is a small chance that your baby might have Trisomy 18. The calculated risk is given on your report.

If there are any changes to your report or if you have any questions, please contact your doctor.

“increased risk of Neural Tube Defect”

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What does it mean?

Information from the South Australian Maternal Serum Screening (SAMS) Program, SA Pathology at Women’s and Children’s Hospital, North Adelaide 1999

If there is anything wrong with your baby, we will inform you.

If the test result is negative, your baby will be born with no abnormality.

If there is a positive result, we will arrange for further tests to be done.

If you have any questions, please contact your doctor.

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Quality Pathology supporting Training and Research

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Second trimester screening of pregnancies for fetal Down syndrome and neural tube defects remains in place and can still be requested as before. We recommend, however, that if a pregnancy is screened in first trimester then any request in second trimester be confined to neural tube defect (NTD) screening only. First trimester screening does not include detection of fetal NTDs.

Requesting first trimester screening
Two request forms are required, one for the blood analysis and one for the ultrasound scan.

BLOOD ANALYSIS
1. 5-10 ml clotted blood sample, taken between 10 and 13 weeks gestation is required. A list of collection centres is provided on the reverse of the SAMSAS request form.
2. Use a SAMSAS request form, telephone (08) 8161 7285 if you require some of these:
   (a) the test request is "first trimester screen";
   (b) complete the gestational age information, the gestation must be between 10+ and 13+ weeks;
   (c) specify the ultrasound practice performing the nuchal translucency scan;
   (d) refer patient to the Privacy Act Disclosure on the SAMSAS request form.
   (e) give the patient the SAMSAS pre-test information booklet;
   (f) send the blood specimen to Women’s and Children’s Hospital, for interstate or remote areas check with SAMSAS on what services are available.

ULTRASOUND
3. Book a Nuchal Translucency scan with the imaging group of choice. The fetus must be between 11+ and 13+ weeks gestation at the time of the scan.
4. Complete an ultrasound request form, specifying "risk of fetal abnormality"; and "Copy to SAMSAS". To comply with National Privacy Legislation, refer patient to the Privacy Act Disclosure on the SAMSAS request form.

SAMSAS will coordinate the results with the ultrasound practice and you will receive a single report giving the risks calculated for the pregnancy. Post-test information booklets are provided with all reports issued by SAMSAS on pregnancies found at increased risk of fetal abnormality.

Availability of first trimester screening
Combined ultrasound and biochemistry screening is not at present offered through all hospitals/clinics. Check with the hospital/clinic concerned.

Costs
For privately insured patients SAMSAS continues its policy of accepting ‘Medicare only’ for the serum biochemistry analyses. There may be a gap payment for the ultrasound measurement. Check with the practice providing this service.

Robert Coccidione, BAppSc, Med Lab Sc
on behalf of the South Australian Maternal Serum Antenatal Screening (SAMSAS) Programme

Gestational Age Windows for Antenatal Screening for Birth Defects

<table>
<thead>
<tr>
<th>First Trimester</th>
<th>Blood sample</th>
<th>10w0d – 13w0d</th>
<th>Ultrasound</th>
<th>11w0d – 13w0d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Trimester</td>
<td>Blood sample</td>
<td>14w0d – 20w0d</td>
<td></td>
<td></td>
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</tbody>
</table>
Screening

“the systematic application of a test procedure to identify individuals at sufficient risk to warrant diagnostic investigations”

• CVS 12 wks
• Amniocentesis 15+wks
• Morphology Ultrasound 18+wks

Aim is to maximise detection of affected pregnancies and minimise false +ves
### Markers; 1st Trimester 2nd Trimester Integrated Test

<table>
<thead>
<tr>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>Integrated Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>free β hCG</td>
<td>free β hCG</td>
<td>free β hCG</td>
</tr>
<tr>
<td>uE3</td>
<td>uE3</td>
<td>uE3</td>
</tr>
<tr>
<td>Papp-A</td>
<td>Papp-A</td>
<td></td>
</tr>
<tr>
<td>Nuchal Translucency</td>
<td>Nuchal Translucency</td>
<td></td>
</tr>
</tbody>
</table>

### Other Markers;

- Maternal age
- Gestational age
- Other Variables
• Fetus must occupy 3/4 of the image
• Fetus must be in a Neutral position
• Hyperextension of fetal neck can increase the NT by 0.6 mm
• Flexion of the neck can decrease the NT by 0.4 mm
• Umbilical cord round the fetal neck (5-10% of cases) can increase the NT by 0.8 mm
• Amniotic membrane and Nuchal membrane must be separate
• Measure the max thickness of the subcutaneous translucency
Increased nuchal translucency and exomphalos in a trisomy 18 fetus at 12 weeks of gestation
Turners syndrome - cystic hygroma
Severe asymmetrical growth restriction in a 13-week fetus with triploidy.
NUCHAL TRANSLUCENCY

- NT is an ultrasonographic feature visible in 1st Tr of pregnancy

- NT results from an accumulation of fluid at the base of fetal neck

- NT thickness increases with GA (0.8 to 1.6 mm)

- Non specific marker,

  thickness >2.5\(^{3.0}\) mm associated with an increased risk of aneuploidy, cardiovascular & pulmonary defects, skeletal dysplasia, renal, metabolic defects & congenital infections & fetal demise.
- Population Medians / MoM
- Gestational Age
- Maternal Age
- Recurrence Risk
- Singleton vs Twins
- Maternal Weight
- Ethnicity
- Diabetes
- Smoking
- Analytical Imprecision
- Risk Calculation ~ NT ~ Biochemistry ~ Combined ~ Integrated
FIRST TRIMESTER SCREEN - INCREASED RISK REPORT

AMENDED REPORT, replaces rep. 09 Apr 2009 15:11

SAMSAS Lab. No. 415790
Gestational Age: 13w6d by Crown Rump Length (Estimated on 07/12/09)
Sample Date: 17/11/2008
Requesting Doctor: Blank2
Referring Lab. No.

First trimester Screen:
- Free beta hCG: 3.23 MoM
- PAPP-A: 0.26 MoM
- NT: 14.4 mm (95th perc. 10.0 mm)
- Down Syndrome Risk odds at Time of Screen: 1:58
- Trisomy 18 Risk odds at Time of Screen: 1:8111
- Trisomy 13 Risk odds at Time of Screen: 1:5908

Risk of Down syndrome: at increased risk (risk: 1:53 at Time of Screen)
Risk of Trisomy 18: not at increased risk (risk: 1:18160 at Time of Screen)

The fetus is at increased risk of aneuploidy based on biochemical and nuchal translucency measurements (cut-off risk: 1:250). CVS or amniocentesis for karyotyping should be considered.

If the patient opts for amniocentesis, please collect a second trimester blood sample at 14+ weeks before the amnio procedure. SAMSAS Study forms enclosed. Call SAMSAS on 08 8161 7285 for additional copies.

Nuchal Translucency scan by Limestone Imaging 08 8723 1050

Copies sent to:
IMVS Call Centre

Doctors

Dr Blank2
C/O Chemical Pathology
SAMSAS

SECOND TRIMESTER SCREEN - INCREASED RISK REPORT

AMENDED REPORT, replaces rep. 09 Apr 2009 15:27

SAMSAS Lab. No. 424820
Gestational Age: 17w2d by Crown Rump Length (Estimated on 12/09)
Sample Date: 17/12/2008
Requesting Doctor: Blank2
Referring Lab. No.

First trimester Screen:
- Free beta hCG: 4.20 MoM
- NT: 1.75 MoM

Risk of Down syndrome: at increased risk (risk: 1:30)
For Aneuploidy risks see First Trimester report, SAMSAS Lab No.: 415790, requesting Dr. Dr Blank2, ph: 8161 7285

Increased risk of open neural tube defect. (AFP > 2.5 MoM). A detailed ultrasound examination of the fetus is advised to exclude NTD, gastroschisis or other structural abnormality, or signs of chromosomal disorders particularly trisomy 13 and triploidy, or fetal loss. *Please provide missing or correct information as per footnote.

Copies sent to:

Dr Blank2
C/O Chemical Pathology
SAMSAS

* ACCURATE GESTATIONAL AGE, MATERNAL AGE, AGE OF DONOR EGG, WEIGHT, SAMPLE DATE, ETHNICITY, NUCHAL TRANSLUCENCY & other pregnancy complications as shown above are required for optimum interpretation. Please contact SAMSAS on 08 8161 7285 for immediate re-calculation of risk and amended report if this OR any data should be different from that shown.

USE OF SAMSAS REQUEST FORMS IMPROVES TESTING EFFICIENCY. PLEASE ENSURE NEURAL TRANSLUCENCY REQUESTS INCLUDE:

"COPY TO SAMSAS"
First trimester Blood samples valid from 6-12wks. Second trimester Blood samples valid from 14-20wks. Nuchal translucency valid from 11-13wks.

This report printed: 9 April 2009 @ 3:23 pm, by: coocianon

Dr Janine Fletcher FRACP FRCPA Biochemical Geneticist/Clinical Geneticist

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samsas@health.sa.gov.au
www.sapathology.sa.gov.au

Quality Pathology supporting Training and Research

Quality Pathology supporting Training and Research
### Screening for trisomy 21

#### Effectiveness of different methods of screening

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<tr>
<th>Method of screening</th>
<th>Detection rate</th>
<th>Number detected</th>
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<tbody>
<tr>
<td>Maternal age</td>
<td>30%</td>
<td>60</td>
</tr>
<tr>
<td>Serum biochemistry at 16 wks</td>
<td>65%</td>
<td>130</td>
</tr>
<tr>
<td>Nuchal translucency (NT) at 12 wks</td>
<td>75%</td>
<td>150</td>
</tr>
<tr>
<td>Fetal NT &amp; β-hCG &amp; PAPP- A at 12 wks</td>
<td>*90%</td>
<td>180</td>
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</tbody>
</table>

* 2.5% Screen positive

**Integrated Test**

Procedure related fetal loss rates are difficult figures to obtain. Corrections need to be made for the background spontaneous fetal loss.
Background Risk

Gestational age

Snijders et al. 1995

Nicolaides et al., The 11-14-week scan, London 1999
Assessment of Risk

Previous Chromosomal Abnormality

- Trisomy 21
- Trisomy 18
- Trisomy 13
- Age
- Risk + 0.75%

- 45XO
- 47XXY/XXX
- Triploidy

0.75%
Marker Levels Change Significantly with Gestation

Measured levels are converted to **Multiples Of the Population Median or MoM values.**

\[
1 \text{ MoM} = \text{Reference for all markers}
\]

**beta hCG at 10 wks GA**

**Patient** \[
120 \text{ IU/L} = 2 \text{ multiples}
\]

**Median** \[
60 \text{ IU/L}
\]

*MoM values are independent of gestational age and concentration Units*

*LogMoM values are used in calculations as they exhibit a Gaussian distribution (Mean +/- SD)*
<table>
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<tr>
<th>Adjustments</th>
<th>AFP_MoM 1st</th>
<th>AFP_MoM 2nd</th>
<th>Beta_MoM 1st</th>
<th>Beta_MoM 2nd</th>
<th>PappA_MoM</th>
<th>Ue3_MoM</th>
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<td>IVF</td>
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<td>/1.093</td>
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<tr>
<td>Previous T21</td>
<td></td>
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<td></td>
<td>+0.75% to T21 Risk odds</td>
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<tr>
<td>Previous T18/T13</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+0.75% to T18 Risk odds</td>
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<tr>
<td>Previous T21 + T18/T13</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+0.75% to both odds</td>
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</tbody>
</table>
Maternal Weight

Unaffected 1st Trimester

Increasing Incidence of Twins

(1990–2003) 1:70 to 1:55

* Assisted reproduction

* Rate of twinning increases with age.

>20% (2006) of pregnancies are now to women 35yrs or over, up from <9% in 1990.
Twins Management

- Screening and Chorionicity
- Nuchal discordance (mono and dichorionic)
- Diagnostic tests (CVS and Amniocentesis)
- Selective feticide
- Twin to twin transfusion
- Laser ablation of vessels
- Delivery
Triploidy 2nd Trimester

(T18 2nd Trimester)

(T21 2nd Trimester)

(GA Overestimate) Turners 2nd Trimester

Diandric Digynic
## RISKS

1. **Open Neural Tube Defects (NTD)**
2. **Down syndrome / Aneuploidy**
3. **Other**

### NTD
- 2nd Trimester
- $\uparrow$ AFP $\geq$ 2 MoM
- Independent of Maternal Age
- Morphology scan

### Down syndrome / Aneuploidy
- 1st & 2nd Trimester
- $\uparrow$ Risk $\geq$ 1 in 300
- Age Dependent
- CVS / Amnio

~ 1/30 will have a NTD

~ 1/20 or 1/40 will have DS

### Other
- Not NTD & Not DS:
  - AFP $< 2$ MoM & DS risk is $< 1$ in 300
  - But
  - **Biochemical results fall outside the Normal expected.**
### Not NTD & Not Downs Profiles

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester N= 26,914</th>
<th>2nd Trimester N= 35,649</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Downs</td>
<td>N= 206 (0.77%)</td>
<td>N= 123 (0.35%)</td>
</tr>
</tbody>
</table>

Total N = 329 (0.53%)

### OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOT KNOWN</td>
<td>N= 25</td>
<td>(7.6%)</td>
</tr>
<tr>
<td>NORMAL</td>
<td>N= 103</td>
<td>(31.3%)</td>
</tr>
<tr>
<td>FETAL DEATH</td>
<td>N= 171</td>
<td>(52%)</td>
</tr>
<tr>
<td>ABNORMAL</td>
<td>N= 30</td>
<td>(9.1%)</td>
</tr>
</tbody>
</table>

- 9 x Triploidy
- 9 x T18
- 3 x T15, 3 x Anenceph.
- 2 x Turners, 2 x Mult. Abn.
- 2 x Metabolic
1st Trimester ? Fail

Not viable at time of screen.
No NT measured

- N= 149
- Not Known= 4
- Normal= 2 (Obese–no NT)
- Fetal Death= 137
- Abnormal= 6 (1xTriploidy,2xXO,2xT15,1xAnencephaly)

Anomalies Found 143/145
Odds 1/1 (98.6%)

2nd Trimester ? Fail

Not viable at time of screen.

- N= 24
- Not Known= 2
- Normal= 0
- Fetal Death= 18
- Abnormal= 4 (2xT18,1xAnencephaly,1xMultiple Con. Abn.)

Anomalies Found 22/22
Odds 1/1 (100%)
1st Trimester Not Downs

Viable at time of screen.

- N= 57
- Not Known= 7
- Normal= 39
- Fetal Death= 3
- Abnormal= 8 (4xTriploidy, 1xT18, 1xOther, 1xAnencephaly, 1xRenal)

Anomalies Found 11/50

Odds 1/4.5 (22%)

2nd Trimester Not NTD Not Downs

Viable at time of screen.

- N= 99
- Not Known= 12
- Normal= 62
- Fetal Death= 13
- Abnormal= 12 (4xTrip., 6xT18, 1xMultiple Con. Abn., 1xMetabolic)

Anomalies Found 25/87

Odds 1/3.5 (28.6%)
Missed 1st Trimester Fetal Deaths

Missed 2nd Trimester Fetal Deaths

1st Trimester Not Downs

2nd Trimester Not NTD Not Downs
The best way to detect these pregnancies is through discriminatory algorithms and distributions, utilizing multiple markers.

\[ Y = 0.425 \ln(\text{beta}_\text{MoM}) - 0.631 \ln(\text{Papp-a}_\text{MoM}) + 0.761 \ln(\text{NT}_\text{MoM}) \]
### What does a risk report mean?

<table>
<thead>
<tr>
<th></th>
<th>% Recall</th>
<th>% Det.</th>
<th>Odds Adverse Outcome</th>
<th>Odds Affected</th>
<th>Miss Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Tr Raised NTD Risk</td>
<td>3%</td>
<td>&gt;90%</td>
<td>1 / 8</td>
<td>1 / 30</td>
<td>1 / 10,000</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Tr Raised DS Risk</td>
<td>5%</td>
<td>65%</td>
<td>1 / 30</td>
<td>1 / 50</td>
<td>1 / 2,500</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Tr Raised DS Risk</td>
<td>5%</td>
<td>90%</td>
<td>1 / 10</td>
<td>1 / 15</td>
<td>1 / 3,500</td>
</tr>
<tr>
<td>Not NTD Not Downs ? Viability</td>
<td>0.5%</td>
<td>75%</td>
<td>1 / 4</td>
<td></td>
<td>1 / 500</td>
</tr>
</tbody>
</table>

Reassurance of ≥ 99.8 % & Anomaly Risk of 2.0 – 25%

Summary data ~ SAMSAS yearly audits SA Birth defects Register Reports
DS Risk = Mat. Age Risk \times LR
DS Risk = Mat. Age Risk x LR

Y = 0.425*ln_beta_MoM – 0.631*ln_Papp-a_MoM + 0.761*ln_NT_MoM

LR_{aff} = \frac{h2}{h1}

Unaffected

Affected

Detection Rate

False -ve

False +ve’s

Discriminatory Variable
DS Risk = Mat. Age Risk × LR

- 20 yrs = 1 in 1600 × 2 = 1 in 800
- 30 yrs = 1 in 1100 × 2 = 1 in 550
- 35 yrs = 1 in 500 × 2 = 1 in 250
- 40 yrs = 1 in 156 × 2 = 1 in 78
- 45 yrs = 1 in 40 × 2 = 1 in 20
Age Specific Performance
Comparison of 1st and 2nd Trimester Screening.
Maternal Age vs Recall and Detection

Maternal Age at Delivery
BENEFITS OF AN EARLY SCAN

• confirms the fetus is alive
• permits accurate dating of pregnancy
• allows early diagnosis of multiple pregnancy & chorionicity
• detects major structural abnormalities and missed abortion
Why did we introduce 1\textsuperscript{st} trimester combined screening into SA?
# Down Syndrome

<table>
<thead>
<tr>
<th>2nd Tr</th>
<th>Detect</th>
<th>Recall</th>
<th>%≥35</th>
<th>%PG≥30</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>91-95</td>
<td>63%</td>
<td>4.9%</td>
<td>9%</td>
<td>20%</td>
<td>28</td>
</tr>
<tr>
<td>96-00</td>
<td>76.7%</td>
<td>6.6%</td>
<td>15%</td>
<td>30%</td>
<td>29</td>
</tr>
<tr>
<td>01-03</td>
<td>76.7%</td>
<td>7.4%</td>
<td>17%</td>
<td>35%</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1st Tr</th>
<th>Detect</th>
<th>Recall</th>
<th>%≥35</th>
<th>%PG≥30</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90.9%</td>
<td>4.9%</td>
<td>25%</td>
<td></td>
<td>31.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IntG</th>
<th>Detect</th>
<th>Recall</th>
<th>%≥35</th>
<th>%PG≥30</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90.9%</td>
<td>2.5%</td>
<td>22%</td>
<td></td>
<td>31.2</td>
</tr>
</tbody>
</table>

*Combining first and second trimester markers for Down syndrome screening: Think twice*

Robert Cocciolone, Kate Brameld, Peter O'Leary, Eric Haan, Peter Muller, Karen Shand

Advantages of 1st trimester screening

- benefits of an early scan
- less false +ves & -ves
- less normal fetuses lost
- higher detection
- personal benefits to patients from earlier diagnosis

Disadvantages

- cost of the nuchal translucency scan
- logistically more difficult to manage
Logistical considerations?

1TR & 2TR screening will coexist.

Management of reports & requests.

How many risks, by whom and when?

Audits and ongoing programme evaluation.
How can these be addressed?

Centralised service & database for,
- all patient demographics
- biochemical results
- NT measurements & providers
- reporting
- recalculation of risks
- retrievable data for analysis

Logical software - risks linked to gestation (1TR & 2TR algorithms)
Trends in state/based Down syndrome screening and invasive prenatal testing with the introduction of first trimester combined Down syndrome, South Australia 1995-2005

Muller PR, Cocciolone R, Haan EA, et al

Utilization of maternal serum Down syndrome screening % of all confinements

69-79%
Utilization of second trimester maternal serum (Δ) and first trimester combined Down syndrome screening (□), % of all confinements

* P < 0.001
% confinements $\geq 35$ years (●) of age vs % of confinements undergoing invasive prenatal tests (△)

* P < 0.001
Confinements ≥ 35 years of age undergoing invasive prenatal tests

% of confinements ≥ 35 years of age with invasive prenatal test

* P < 0.001

43%

* 24.8%

% 50 45 40 35 30 25 20 15 10 5 0

0 10 20 30 40 50


Year
Number of invasive prenatal tests to detect one DS fetus

<table>
<thead>
<tr>
<th>Year</th>
<th>Down syndrome cases</th>
<th>Rate of DS per invasive procedure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>32</td>
<td>1/86</td>
</tr>
<tr>
<td>1996</td>
<td>32</td>
<td>1/94</td>
</tr>
<tr>
<td>1997</td>
<td>41</td>
<td>1/83</td>
</tr>
<tr>
<td>1998</td>
<td>46</td>
<td>1/61</td>
</tr>
<tr>
<td>1999</td>
<td>42</td>
<td>1/71</td>
</tr>
<tr>
<td>2000</td>
<td>37</td>
<td>1/79</td>
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<tr>
<td>2001</td>
<td>36</td>
<td>1/90</td>
</tr>
<tr>
<td>2002</td>
<td>44</td>
<td>1/66</td>
</tr>
<tr>
<td>2003</td>
<td>42</td>
<td>1/46</td>
</tr>
<tr>
<td>2004</td>
<td>34</td>
<td>1/49</td>
</tr>
<tr>
<td>2005</td>
<td>47</td>
<td>1/40 *</td>
</tr>
</tbody>
</table>

*p < 0.001
Number of invasive prenatal tests to detect one aneuploid fetus

<table>
<thead>
<tr>
<th>Year</th>
<th>Aneuploidy cases</th>
<th>Rate of aneuploidy per invasive procedure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>51</td>
<td>1/35</td>
</tr>
<tr>
<td>1996</td>
<td>46</td>
<td>1/47</td>
</tr>
<tr>
<td>1997</td>
<td>50</td>
<td>1/38</td>
</tr>
<tr>
<td>1998</td>
<td>65</td>
<td>1/31</td>
</tr>
<tr>
<td>1999</td>
<td>60</td>
<td>1/33</td>
</tr>
<tr>
<td>2000</td>
<td>56</td>
<td>1/32</td>
</tr>
<tr>
<td>2001</td>
<td>55</td>
<td>1/30</td>
</tr>
<tr>
<td>2002</td>
<td>55</td>
<td>1/32</td>
</tr>
<tr>
<td>2003</td>
<td>64</td>
<td>1/24</td>
</tr>
<tr>
<td>2004</td>
<td>65</td>
<td>1/21</td>
</tr>
<tr>
<td>2005</td>
<td>91</td>
<td>1/15</td>
</tr>
</tbody>
</table>

* p < 0.001
## Overall Prenatal Detected Down Syndrome cases (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Down syndrome cases</th>
<th>Prenatal detected DS cases (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>32</td>
<td>71.9</td>
</tr>
<tr>
<td>1996</td>
<td>32</td>
<td>81.3</td>
</tr>
<tr>
<td>1997</td>
<td>41</td>
<td>70.7</td>
</tr>
<tr>
<td>1998</td>
<td>46</td>
<td>73.9</td>
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<tr>
<td>1999</td>
<td>42</td>
<td>71.4</td>
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<td>37</td>
<td>70.3</td>
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<td>2001</td>
<td>36</td>
<td>58.3</td>
</tr>
<tr>
<td>2002</td>
<td>44</td>
<td>65.9</td>
</tr>
<tr>
<td>2003</td>
<td>42</td>
<td>81.0</td>
</tr>
<tr>
<td>2004</td>
<td>34</td>
<td>88.2</td>
</tr>
<tr>
<td>2005</td>
<td>47</td>
<td>83.0</td>
</tr>
</tbody>
</table>

** p = 0.21
• Demonstrated an improved efficiency in the utilization of invasive prenatal tests

• Despite the increase in gravid women ≥ 35 years of age the number of invasive prenatal tests in this age group has significantly declined

• Despite the significant decrease in invasive prenatal tests the overall antenatal detection of Down syndrome did not decrease, and appears to increase once the utilization of first trimester combined Down syndrome screening reaches > 30% of confinements
To review changes in the utilization and effectiveness of state/population-based antenatal screening for NTDs in South Australia from 1986 to 2004
<table>
<thead>
<tr>
<th>Year</th>
<th>Average births/Yr (#)</th>
<th>Average NTDs/Yr (#)</th>
<th>Overall antenatal detection of NTD(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-91</td>
<td>19,714</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>1992-98</td>
<td>19,437</td>
<td>32*</td>
<td>88.8</td>
</tr>
<tr>
<td>1999-2004</td>
<td>17,867</td>
<td>24</td>
<td>94.5 **</td>
</tr>
</tbody>
</table>

*State-wide educational drive on the benefits of Folic Acid supplementation for the reduction of NTDs 1994

** p<0.001
Despite a significant decrease in the utilization of MSAFP screening, the population-based detection of NTDs has increased significantly in South Australia.

The decreased utilization of second trimester MSAFP represents improve clinician confidence in second trimester ultrasound for the detection of NTDs
future directions

- new biochemical markers
- fetal cells in maternal circulation
- fetal DNA in maternal circulation
- complex protein profiles - mass spectrometry
• **ADAM12 (A Disintegrin And Metalloprotease)** is a multidomain Zn containing protein with protease, cell adhesion and signaling activity.

• Researchers focus on ADAMs has been asthma, alzheimers and cancer (breast, liver, colon)

• ADAM12 cleaves IGFBP-3 & 5 and may regulate the bioavailability of IGF (PAPP-A cleaves IGFBP-4)

• Overall, it appears that ADAMs are expressed during growth and development.

• Human placenta expresses very high levels of ADAM12

• Is it useful in MSS programs?
y = 0.00009011x² - 0.02431198x + 2.25980095
R² = 0.20802869
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cases</th>
<th>Uncorrected Median ng/ml / MoM</th>
<th>Median Weight kg</th>
<th>Weight corrected Median MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td>?</td>
<td>4385</td>
<td>597 / 0.99</td>
<td>68</td>
<td>0.98</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>94</td>
<td>597 / 0.89</td>
<td>73</td>
<td>0.95</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>71</td>
<td>994 / 1.15</td>
<td>65</td>
<td>1.12</td>
</tr>
<tr>
<td>Caucasian</td>
<td>5604</td>
<td>562 / 0.99</td>
<td>68</td>
<td>1.0</td>
</tr>
<tr>
<td>Oriental</td>
<td>153</td>
<td>788 / 1.28</td>
<td>55</td>
<td>1.10</td>
</tr>
<tr>
<td>South Asian</td>
<td>419</td>
<td>738 / 1.12</td>
<td>56.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Total/Median</td>
<td>10726</td>
<td>587 / 1.0</td>
<td>67</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Weight (kg)</td>
<td>ADAM12 MoM uncorrected</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>-------------</td>
<td>-------------------------</td>
<td></td>
</tr>
<tr>
<td>IDDM</td>
<td>43</td>
<td>74</td>
<td>0.76</td>
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<tr>
<td>Smoker</td>
<td>758</td>
<td>70</td>
<td>0.86</td>
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<tr>
<td>IVF</td>
<td>493</td>
<td>70</td>
<td>0.94</td>
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</tr>
<tr>
<td>Twins</td>
<td>227</td>
<td>69</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>All ADAMs</td>
<td>First Trimester</td>
<td>Second Trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>-----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detection Rate</td>
<td>Detection Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% (no)</td>
<td>% (no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gest’n Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 82 (N=3648)</td>
<td>83 – 97 (N=8579)</td>
<td>63 – 97 (N=12227)</td>
<td>98 – 140 (N=2941)</td>
<td></td>
</tr>
<tr>
<td>FPR</td>
<td>1st Tr Combined</td>
<td>1st Tr Combined + ADAM12</td>
<td>1st Tr Combined</td>
<td>1st Tr Combined + ADAM12</td>
</tr>
<tr>
<td>3%</td>
<td>92.9 (39/42)</td>
<td>95.2 (40/42)</td>
<td>79.0 (53/67)</td>
<td>74.6 (50/67)</td>
</tr>
<tr>
<td>5%</td>
<td>95.2 (40/42)</td>
<td>97.6 (41/42)</td>
<td>89.6 (60/67)</td>
<td>86.6 (58/67)</td>
</tr>
<tr>
<td>7%</td>
<td>100 (42/42)</td>
<td>100 (42/42)</td>
<td>92.5 (62/67)</td>
<td>89.6 (60/67)</td>
</tr>
<tr>
<td>Pros ADAMs</td>
<td>First Trimester</td>
<td>Second Trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
<td>------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detection Rate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>% (no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gest’n Days</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤ 82</td>
<td>83 – 97</td>
<td>63 – 97</td>
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<tr>
<td>(N= 3648)</td>
<td>(N=8579)</td>
<td>(N=12227)</td>
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<tr>
<td>FPR</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Tr Combined</td>
<td></td>
<td>1st Tr Combined</td>
<td>1st Tr Combined</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3%</td>
<td>81.8 (9/11)</td>
<td>77.3 (17/22)</td>
<td>81.8 (27/33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90.9 (10/11)</td>
<td>(18/22)</td>
<td>(27/33)</td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>90.9 (10/11)</td>
<td>95.5 (21/22)</td>
<td>97.0 (32/33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 (11/11)</td>
<td>(21/22)</td>
<td>(32/33)</td>
<td></td>
</tr>
<tr>
<td>7%</td>
<td>100 (11/11)</td>
<td>95.5 (21/22)</td>
<td>97.0 (32/33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 (11/11)</td>
<td>(21/22)</td>
<td>(32/33)</td>
<td></td>
</tr>
<tr>
<td>All aff</td>
<td>42</td>
<td>67</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.7 (6/7)</td>
<td>85.7 (6/7)</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>
• All current publications are based on measurements from frozen samples

• Might be useful: 9-10wks, Valinen 2009, Spencer 2007

• No advantage: 11-13wks Poon 2009

• Could be considered in multi-marker combinations: 2nd Tr Donaldson 2008
  ↑DR 2-3% and ↓FPR 0.9-1.7%

• Other pregnancy complications: ↓ in IUGR/SGA Cowans & Spencer 2007,
  ↓ in PE Laigaard 2005
  ? IVF Laigaard 2009
SUMMARY

• ADAM12 levels affected by mat. wt, ethnicity, IDDM, smoking, Twins, IVF
• ADAM12 levels increase with gestation in normal pregnancies
• ADAM12 med MoM increases with gestation in affected T21 pregnancies
• In T21 pregnancies ADAM12 levels are low in early 1st Tr, equivocal in mid to late 1st Tr and elevated in 2nd trimester
• 9-11w ~ 2.3-2.4% ↑DR with ADAM12 at a 3-5% FPR
• 12-13w+6d performance drops with ADAM12
• 9-13w+6d no advantage in using ADAM12
• 14-20w MSS performance improves with ADAM12
• Improved performance can be translated to either ↑DR for a fixed FPR or to ↓FPR for a fixed risk cut off
• Larger prospective studies are needed to further assess its value in MSS programs